

BIOGRAPHICAL SKETCH

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NAME: **Zang, Mengwei**

eRA COMMONS USER NAME (credential, e.g., agency login): **mwzang1@bu.edu**

POSITION TITLE: **Associate Professor, University of Texas Health Science Center at San Antonio**

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Wannan Medical College, China	MD	1984	Clinical Medicine
Henan Medical University, China	MS	1987	Pathophysiology
Chinese Academy of Medical Sciences	PhD	1998	Pharmacology/Signal Transduction
Mayo Clinic and Foundation	Post-doc	1998-1999	Gastroenterology & Molecular Pharmacology
Boston University School of Medicine	Post-doc	1999-2003	Diabetes/Signal Transduction

A. PERSONAL STATEMENT

My research focuses on elucidating the pathogenesis of diabetes and developing innovative approaches to this common metabolic disease which is associated with significant morbidity and mortality. My laboratory's research is focused on: 1) The identification of new nutrient sensors and hormones in the regulation of glucose and lipid metabolism; 2) The elucidation of pathological mechanisms of metabolic diseases including obesity, insulin resistance, type 2 diabetes, non-alcoholic and alcoholic fatty liver diseases, and atherosclerosis; and 3) The identification and characterization of novel drug targets and their small molecule agents for the treatment of metabolic disease. My major findings include the discovery of novel drug targets for metabolic disease, including AMPK and mTORC1, the NAD-dependent deacetylase SIRT1, the transcription factor SREBP, the nuclear receptor—retinoic acid receptor, and the hepatocyte-derived hormone FGF21. My work has pioneered to demonstrate the pivotal role of lipogenesis in the development of systemic insulin resistance and fatty liver disease, leading to a number of original manuscripts in high impact journals including *Cell Metabolism*, *Gastroenterology*, *Diabetes*, etc., 5 of which have been cited more than 400 times. The long-term goal of my laboratory is to understand the mechanisms for the fundamental regulation of nutrient metabolism in health and disease. I also serve as a permanent member for NIH/NIDDK study sections such as NIH T32 training grants. I have mentored 20 postdoctoral fellows and graduate students as well as a number of other graduate rotation, undergraduate and summer students for more than 15 years. I serve as a co-leader to the Pilot and Feasibility Core of the Diabetes Research Center at UTHSCSA. I am highly committed to mentoring a PhD student in Xiangya Medical School Research Program of UTHSCSA.

1. **Zang M**, Xu S, Maitland-Toolan KA, Zuccollo A, Hou X, Jiang B, Wierzbicki M, Verbeuren TJ, Cohen RA. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherogenesis in diabetic LDL receptor-deficient mice. *Diabetes*. 2006; 55: 2180-2191. ([497 citations, Google Scholar](#))
2. Li Y, Xu S, Mihaylova M, Zheng B, Hou X, Jiang B, Park O, Luo Z, Lefai E, Shyy JY, Gao B, Wierzbicki M, Verbeuren TJ, Shaw RJ, Cohen RA, **Zang M**. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin resistant mice. *Cell Metabolism*. 2011; 13: 376-388. ([493 citations, Google Scholar](#))
3. Li Y, Wong K, Giles A, Lee JW, Jiang J, Adams AC, Kharitonov A, Yang Q, Gao B, Guarente L, **Zang M**. Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. *Gastroenterology*. 2014; 146: 539–549.
4. Luo T, Nocon A, Fry J, Sherban A, Rui X, Jiang B, Xu XJ, Han J, Yan Y, Yang Q, Li Q, **Zang M**. AMPK activation by metformin suppresses abnormal adipose tissue extracellular matrix remodeling and ameliorates insulin resistance in obesity. *Diabetes*, 2016; 65:2295-2310.

B. POSITIONS AND HONORS

Positions and Employment

1987-1993	Lecturer and Assistant Professor , Wannan Medical College, Anhui, China
1994-1995	Associate Professor , Department of Pathophysiology, Wannan Medical College, Anhui, China
1995-1998	Associate Professor , Department of Pharmacology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
2004-2010	Assistant Professor , Department of Medicine, Boston University School of Medicine, Boston
2011-2016	Associate Professor , Department of Medicine, Boston University School of Medicine, Boston
2016-	Associate Professor with Tenure , Barshop Institute for Longevity and Aging Studies, Department of Molecular Medicine, University of Texas Health Science Center at San Antonio
2016-	The Ewing Halsell Distinguished Chair in Aging Research, University of Texas Health Science Center at San Antonio
2016-	Research Health Scientist , Geriatric Research, Education and Clinical Center (GRECC) for Healthy Aging, South Texas Veterans Health Care System, San Antonio, TX

Other Experience and Professional Memberships

2004-	Member , American Diabetes Association
2009-	Member and Treasurer , Chinese American Diabetes Association
2010-	External reviewer , Grant Review Committee for National Nature Science Foundation of China (NSFC), Grant Review Committees for Diabetes UK, the Food and Health Bureau (FHB) of the Hong Kong SAR Government
2010-2012	Member , American Heart Association Abstract Review Committee, Endothelium, Vascular Tone and Nitric Oxide Section
2010-2014	Permanent member , American Heart Association Grant Review Committee, Molecular Signaling-Basic Science 3
2010-2015	Ad hoc reviewer , NIH Study Sections: Integrative Physiology of Obesity and Diabetes (IPOD) Study Section; NIH/Hepatobiliary Pathophysiology (HBPP); NIDDK Diabetes, Endocrinology and Metabolic Disease (DDK-B)
2012	Chair , the 1 st International Symposium on Liver Inflammation Cancer and New Drug Target Development, Hefei, Anhui, China
2013-2017	Permanent reviewer , NIH/NIDDK Diabetes, Endocrinology and Metabolic Disease (DDK-B) Study Section
2015	Chair , Boston University Evans Center ARC Symposium: Nutrient Sensors and Metabolic Disease, Evans Center, Boston University School of Medicine, Boston, MA
2016	Ad hoc reviewer , NIH Center for Scientific Review Special Emphasis Panel, ZRG1 DKUS-C (82), Toxicology and Digestive, Kidney and Urological Systems AREA Review; ZRG1 DKUS-C (54), R21 Grants for New Investigators to Promote Diversity in Health-Related Research
2017	Ad Hoc Reviewer , NIH Grant Review Committee, Integrative Nutrition and Metabolic Processes (INMP) Study Section; NIH Scientific Review Special Emphasis Panel, ZRG1 EMNR-V, Molecular Mechanisms of Obesity and Diabetes Special Emphasis Panel
2017-2019	Editorial Board , <i>Hepatology</i> , <i>Frontiers in Cardiovascular Metabolism</i> , <i>Plos One</i> and <i>Int J Physiol Pathophysiol Pharmacol</i> .

Honors and Awards

1990	The State Outstanding Teacher Award, Anhui Province People's Government and Higher Education Committee, Anhui Province, P.R. China
1991	The 3 rd Place Prize of National Excellent Master Thesis by Chinese Pathophysiology Society
1991	The Second Place of National Medical Sciences and Technology Advancement Award by Ministry of Health in P. R. China
1998	The National Outstanding Young Scientist Award, Chinese Pharmacological Society
1998	The Outstanding Young Investigator Award, Chinese Society of Neuropharmacology
2000	The Third Place of Outstanding Research Award for Progression in Science and Technology by Beijing People's Government
2006	Travel Award, the 4 th International Symposium on AMPK (FASEB Research Conference)
2009	Robert Dawson Evans Faculty Merit Award, Boston University School of Medicine

2011, 2016	Wing Tat Lee Award, the Dean of Boston University School of Medicine
2015	American Diabetes Association Basic Science Award
2016	Holder of The Ewing Halsell Endowment

C. Contributions to Science

1. Establishing the structural basis of Class II secretin receptors to provide the majority of clinically used GPCR-based therapeutics. My early research career at Mayo Clinic provided mechanistic insight into the structural basis of ligand binding to the secretin receptor, a new family of the G-protein-coupled receptor (GPCR) superfamily. My scientific findings also contributed to the current understanding of the relationship between the structure and function of other GPCRs, e.g., vasoactive intestinal peptide and parathyroid hormone. Given that the secretin receptor has recently been shown to be an important therapeutic target for diabetes and cancer, my pioneer findings advance the progress of GPCR pharmacology and provide the rationale for developing secretin receptor-activating drugs to treat diabetes or pancreatic cancer in humans.

- a. Dong M, Asmann YW, **Zang M**, Pinon DI, Miller LJ. Identification of two pairs of spatially approximated residues within the carboxyl-terminus of secretin and its receptor. *J Biol Chem*. 2000; 275: 26032-26039. PMID: 10859300.
- b. Dong M, **Zang M**, Pinon DI, Li Z, Lybrand TP, Miller LJ. Interaction among four residues distributed through the secretin pharmacophore and a focused region of the secretin receptor amino terminus. *Molecular Endocrinology*. 2002; 16: 2490-2501. PMID: 12403838.
- c. **Zang M**, Dong M, Pinon DI, Ding X, Hadac EM, Miller LJ. Spatial approximation between a photolabile residue in position 13 of secretin and the amino-terminal tail of the secretin receptor. *Molecular Pharmacology*. 2003; 63: 993-1001. PMID: 12695527.

2. Targeting Raf-1-MEK-ERK signaling cascade for the discovery of currently used anti-cancer drugs. My postdoctoral research at Boston University School of Medicine characterized p21-activated kinase (Pak) as a novel upstream kinase of Raf-1 kinase in response to the microtubule depolymerizing drugs. My research was the first to identify the protein-protein interaction between Pak1 and Raf-1 kinases, which provides a new drug target that blocks abnormal Raf-1 activation in a variety of human cancers. My research also uncovered that Pak1-dependent phosphorylation of Raf-1 at Ser338 represents the molecule basis for the cross talk between a Rac-Cdc42-Pak1 pathway and Raf-1-MEK-ERK pathway. Given my early and original findings that the dysregulation of the Raf-1-MEK-ERK cascade is implicated in tumor growth, the Food and Drug Administration (FDA) has currently approved 10 protein kinase inhibitors. These new kinase inhibitors acting via Raf-1-MEK-ERK pathway have been currently used for cancer therapy in humans.

- a. **Zang M**, Waelde CA, Xiang X, Rana A, Wen R, Luo Z. Microtubule integrity regulates Pak leading to Ras-independent activation of Raf-1. *J Biol Chem*. 2001; 276: 25157-25165. PMID: 11274179.
- b. **Zang M**, Hayne C, Luo Z. Interaction between active Pak1 and Raf-1 is necessary for phosphorylation and activation of Raf-1. *J Biol Chem*. 2002; 277: 4395-4405. PMID: 11733498.
- c. **Zang M**, Gong J, Luo L, Zhou J, Xiang X, Huang W, Huang Q, Luo X, Olbrot M, Peng Y, Chen C, Luo Z. Characterization of S338 phosphorylation for Raf-1 activation. *J Biol Chem*. 2008; 283: 31429-31437. PMCID: PMC2581588.

3. Discovering the molecular connection between two nutrient sensors, SIRT1 and AMPK, laying the groundwork for new pharmacological intervention of fatty liver disease, insulin resistance, and vascular complications in diabetes. Epidemiological studies suggest that the long-term consumption of diets rich in polyphenols protect against cardiovascular diseases, diabetes, and cancers. However, their mechanism(s) of action remains a mystery, limiting their therapeutic potential. In collaboration with an international Servier Pharmaceutical Company, my laboratory's studies: 1) revealed that inactivation of the energy sensor AMP-activated protein kinase (AMPK) in the liver contributes to the pathogenesis of hyperlipidemia and type 1 diabetes; 2) defined the molecular mechanism by which polyphenols prevent fatty liver disease and vascular dysfunction associated with diabetes; and 3) emphasized a new therapeutic avenue with polyphenols for hyperlipidemia and atherosclerosis in type 1 and type 2 diabetes. My laboratory has been widely recognized as the first to demonstrate that activation of the nutrient sensors, the NAD-dependent deacetylase SIRT1 and AMPK, represents a novel mechanism for the beneficial effects of natural polyphenols on fatty liver disease associated with type 1 and type 2 diabetes. These preclinical studies generate important information relevant to not only the pathogenesis of diabetes and atherosclerosis, but also to the discovery of novel therapeutic drug targets for metabolic disease. Our mechanistic work has contributed significantly to gained knowledge about the

biological functions of polyphenols in human health and disease. Therapeutically, our research has led to pharmaceutical company interest in searching for small molecules that modulate AMPK and SIRT1 for treating metabolic disease and some cancers related to obesity. Two pioneer papers, one published in **Diabetes** and the in **J Biol Chem**, have been cited more than 450 times. Below is a list of several representative publications.

- a. **Zang M**, Xu S, Maitland-Toolan KA, Zuccollo A, Hou X, Jiang B, Wierzbicki M, Verbeuren TJ, Cohen RA. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherogenesis in diabetic LDL receptor-deficient mice. **Diabetes**. 2006; 55: 2180-2191. PMID: 16873680.
- b. Zuccollo A, Shi C, Mastroianni R, Maitland KA, Weisbrod RM, **Zang M**, Xu S, Cayatte A, Corda S, Lavielle G, Verbeuren TJ, Cohen RA. The thromboxane A2 receptor antagonist, S18886, prevents enhanced atherogenesis caused by diabetes mellitus. **Circulation**. 2005; 112: 3001-3008. PMID: 16260636.
- c. Hou X, Xu S, Maitland-Toolan KA, Sato K, Jiang B, Ido Y, Lan F, Walsh K, Wierzbicki M, Verbeuren TJ, Cohen RA, **Zang M**. SIRT1 regulates hepatocyte lipid metabolism through activating AMP-Activated protein kinase. **J Biol Chem**. 2008; 283: 20015-20026. PMCID: PMC2459285. **Faculty of 1000 Biology**
- d. Luo T, Nocon A, Fry J, Sherban A, Rui X, Jiang B, Xu XJ, Han J, Yan Y, Yang Q, Li Q, **Zang M**. AMPK activation by metformin suppresses abnormal adipose tissue extracellular matrix remodeling and ameliorates insulin resistance in obesity. **Diabetes**, 2016; 65:2295-2310. PMID: 27207638.

4. Dissecting mechanisms of fatty liver disease and atherosclerosis in diabetes: protein kinase/phosphorylation, transcription factor/transcription, metabolic regulation, drug targets, and clinical endpoints. One of my laboratory's most critical contributions to science was the identification of the nutrient sensing network involved in the regulation of liver metabolic homeostasis and disease progression. As more than one-third of US adults are currently obese, there is a renewed interest in understanding metabolic reprogramming beyond traditional hormones such as insulin and glucagon. Our research efforts address how a new nutrient sensor is dynamically modulated by nutrient scarcity and availability and how this process is disrupted in metabolic disease. We are approaching these important questions by using genetically modified mouse models, pharmacologically treated animal models, and nutritionally challenged animal models. My laboratory has been widely-recognized as the first to illustrate that the master nutrient sensor AMPK directly phosphorylates and inhibits sterol regulatory element binding protein (SREBP), a key lipogenic transcription factor, and thereby improves hepatic steatosis and aortic atherosclerosis caused by type 2 diabetes. Our translational studies in aortic atherosclerosis in humans, along with well-established porcine model of diabetes-induced atherosclerosis, provide *in vivo* evidence that the dysregulation of AMPK-SREBP contributes to vascular inflammation and atherosclerotic lesion development. These pioneer findings support the new concept that AMPK-dependent phosphorylation of SREBP may offer a therapeutic target for non-alcoholic fatty liver and atherosclerosis associated with diabetes.

- a. **Zang M**, Zuccollo A, Hou X, Nagata D, Walsh K, Herscovitz H, Brecher P, Ruderman NB, Cohen RA. AMP-activated protein kinase is required for the lipid-lowering effect of metformin in insulin-resistant human HepG2 cells. **J Biol Chem**. 2004; 279: 47898-47905. PMID: 15371448.
- b. Li Y, Xu S, Mihaylova M, Zheng B, Hou X, Jiang B, Park O, Luo Z, Lefai E, Shyy JY, Gao B, Wierzbicki M, Verbeuren TJ, Shaw RJ, Cohen RA, **Zang M**. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin resistant mice. **Cell Metabolism**. 2011; 13: 376-388. PMCID: 3086578. **Selected as the most cited article in Cell Metabolism**.
- c. Li Y, Xu S, Jiang B, Cohen RA, **Zang M**. Activation of sterol regulatory element binding protein and NLRP3 inflammasome in atherosclerotic lesion development in diabetic pigs. **PLoS One**, 2013; 8: e67532. doi:10.1371. PMCID: 3692453.

5. Unraveling the nutritional regulation of the liver-derived hormone FGF21 and developing an emerging field of FGF21-based therapeutic approach for fatty liver disease and other metabolic diseases. As the major metabolite of vitamin A, all-trans-retinoic acid (RA) is a natural ligand of retinoic acid receptor (RAR) that is clinically used for anti-cancer therapy. My laboratory has discovered that hepatic RAR acts as a novel component to induce the hepatocyte-derived hormone fibroblast growth factor 21 (FGF21) and regulates lipid metabolism. My laboratory has made this pioneering discovery with newly generated liver-specific SIRT1 knockout mice and further demonstrated that hepatic SIRT1-induced FGF21 production improves hepatic steatosis and increases browning of white adipose tissue. These original findings help establish the hepatocyte-derived endocrine signaling of the SIRT1-FGF21 axis may represent a new therapeutic target for NAFLD and obesity. These studies from my laboratory highlight both basic and potentially translational applications,

accounting for the fact that pharmacological modulators of SIRT1 and FGF21 are currently under active study in clinical trials in humans. Below is a list of several representative publications.

- a. Li Y, Xu S, Giles A, Nakamura K, Lee JW, Hou X, Donmez G, Li J, Luo Z, Walsh K, Guarente L, **Zang M**. Hepatic overexpression of SIRT1 in mice attenuates endoplasmic reticulum stress and insulin resistance in the liver. **FASEB J**. 2011; 25:1664-1679. PMCID: PMC3079300.
- b. Li Y, Wong K, Walsh K, Gao B, **Zang M**. Retinoic acid receptor β stimulates hepatic induction of fibroblast growth factor 21 to promote fatty acid oxidation and control whole-body energy homeostasis in mice. **J Biol Chem**. 2013; 288: 10490-10540. PMCID: PMC3624431.
- c. Li Y, Wong K, Giles A, Lee JW, Jiang J, Adams AC, Kharitonov A, Yang Q, Gao B, Guarente L, **Zang M**. Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. **Gastroenterology**. 2014; 146: 539–549. PMCID: PMC4228483.
- d. Gong Q, Hu Z, Zhang F, Cui A, Chen X, Jiang H, Gao J, Chen X, Han Y, Liang Q, Ye D, Shi L, Eugene Chin Y, Wang Y, Xiao H, Guo F, Liu Y, **Zang M**, Xu A, Li Y. Fibroblast Growth Factor 21 Improves Hepatic Insulin Sensitivity by Inhibiting Mammalian Target of Rapamycin Complex 1. **Hepatology**, 2016; 64:425-438. PMID: 26926384.

List of Published Work in MyBibliography: (A total of ~50, total citations >3000 from Google Scholar)

<https://www.ncbi.nlm.nih.gov/sites/myncbi/1t9lelWbiPVQk/bibliography/48722753/public/?sort=date&direction=descending>

D. RESEARCH SUPPORT

ONGOING SUPPORT

- | | | |
|--|------------------------------|--|
| 1. RO1DK100603
NIH/NIDDK
<i>Retinoic acid receptor, lipid metabolism, and fatty liver disease</i>
The overall objective of this project is to define the metabolic consequences, interventions, and mechanisms of retinoic acid receptor (RAR) and its agonists on hepatic lipogenesis and ER stress in non-alcoholic fatty liver disease (NAFLD). | Mengwei Zang (PI) | 01/01/2015 - 12/31/2018
\$900,000 (Total Direct Cost) |
| 2. Basic Science Award 1-15-BS-216
American Diabetes Association
<i>Retinoic acid receptor functions as a novel regulator of lipid metabolism in type 2 diabetes and obesity</i>
The major goal of this project is to investigate whether activation of retinoic acid receptor has the therapeutic potential for deregulation of metabolic and energy homeostasis in type 2 diabetes and obesity. | Mengwei Zang (PI) | 01/01/2015 - 12/31/2017
\$345,000 (Total Direct Cost) |
| 3. R21AA021181-01 (No Cost Extension)
NIH/NIAAA
<i>mTORC1 activation in alcoholic liver injury</i>
The major goal of this study is to investigate whether mTORC1 plays a role in the development of hepatic ER stress and steatosis in alcoholic liver disease (ALD). | Mengwei Zang (PI) | 09/15/2013 - 08/31/2017
\$250,000 (Total Direct Cost) |
| 4. Start-Up Fund
UTHSCSA
<i>Nutrient Sensing and metabolic disease</i> | Mengwei Zang (PI) | 03/01/2016 – No Expired Day
\$800,000 (Total Direct Cost) |
| 5. Halsell Endowment Fund
UTHSCSA
<i>Aging-related metabolic disease</i> | Mengwei Zang (Holder) | 03/01/2016 – No Expired Day
\$1,450,000 (Endowment Fund) |

Completed Research Support in Past Three Years

- | | | |
|---|--|---|
| 1. RO1DK076942
NIH/NIDDK
<i>Sirt2 regulates AMPK and lipid metabolism in diabetes</i>
The goal of this study is to investigate whether SIRT1 functions as a novel regulator of AMPK to modulate hepatocyte lipid metabolism, non-alcoholic fatty liver disease, and atherosclerosis in diabetes. | Mengwei Zang (PI) | 07/15/2008 - 05/31/2015
\$1,000,000(Total Direct Cost) |
| 2. PO1 HL068758
NIH/NHLBI
<i>SIRT1, Polyphenols, and Endothelial Oxidants</i>
The objective of this project is to study interactions of oxidants, polyphenols, and SIRT1 in endothelial cells | Neil Ruderman (PI)
Project#3 PI: Richard A. Cohen; Co-PI: Mengwei Zang | 04/15/2009 - 01/31/2014
\$6,600,000(Total Direct Cost) |

My lab research is focused on the identification of the regulation of nutrient sensing and metabolism, primarily at the levels of the regulation of protein phosphorylation/deacetylation and gene transcription. Achievements that might be considered “breakthrough” include identifying AMP-activated protein kinase as a “master” nutrient sensor in the regulation of lipid metabolism and identifying the newly discovered hormone—fibroblast growth factor (FGF21)—as a critical regulator of fatty acid oxidation in response to profound fasting. Importantly, we have pioneered to demonstrate that inhibition of hepatic *de novo* lipogenesis could be potential for a new therapeutic approach to combat metabolic disease. Remarkably, our translational research in patients with non-alcoholic fatty liver disease indicates a role of fatty acid metabolic dysregulation in humans with fatty liver disease. However, this field is at a relatively early stage and many aspects remain incompletely understood. Therefore, our ongoing projects are critical to explore the molecular mechanisms by which FGF21 controls lipid metabolism and hepatic steatosis in experimental animals and humans. This is a very exciting angle and an area with mechanistic and translational possibilities. My lab’s experience, resources and available FGF21 transgenic and knockout mice, as well as our active collaborations with leading experts at UTHSCSA and strong support from Department of Molecular Medicine and Barshop create an outstanding and unique environment for training a PhD student of Xiangya Medical School Research Program.